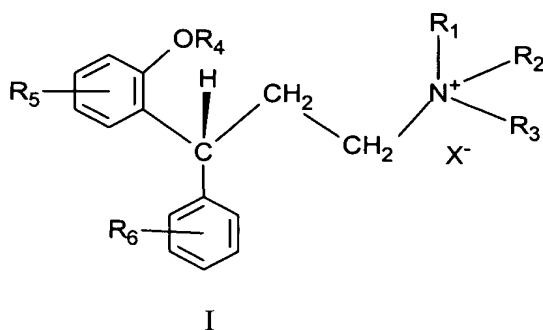


We Claim:

1. A method of treating chronic obstructive pulmonary disease (COPD) in a mammal, comprising administering a first pharmaceutical agent and a second pharmaceutical agent, wherein the first pharmaceutical agent comprises a compound of formula I



or an enantiomer thereof, wherein:

- each R_1 , R_2 , and R_3 is independently H, C_1 - C_5 alkyl optionally substituted with phenyl, or C_2 - C_6 alkenyl; or two of R_1 , R_2 and R_3 may form a ring together with the quaternary ammonium nitrogen;

R_4 is

- H,
-CO- R_{4-1} , where R_{4-1} is
 C_1 - C_4 alkyl,
 C_1 - C_4 alkoxy, or
-NR₄₋₂R₄₋₃, where R_{4-2} and R_{4-3} are the same or different and are
-H or C_1 - C_4 alkyl;

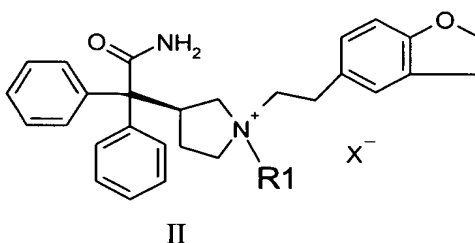
R_5 and R_6 are the same or different and are

- H;
 C_1 - C_4 alkyl optionally substituted with 1 or 2
-OH,
 C_1 - C_4 alkoxy,
-COOH, or
-CO-O-(C_1 - C_3 alkoxy);
-F, -Cl, or Br; or
-CF₃;

where X^- is an anion of hydrochloric acid; hydrobromic acid; hydroiodic acid; sulfuric acid; phosphoric acid; nitric acid; citric acid; methanesulfonic acid; $CH_3-(CH_2)_n-COOH$ where n is 0 to 4; $HOOC-(CH_2)_m-COOH$, where m is 1 to 4; $HOOC-CH=CH-COOH$; or benzoic acid; and

- 5 the second pharmaceutical agent is an Adenosine A_{2a} Receptor Agonist, a D2-Dopamine Receptor Agonist, a PDE Inhibitor, a corticosteroid, a norepinephrine reuptake inhibitor, or 4-hydroxy-7-[2-[2-[3-[2-phenylethoxy]-propylsulphonyl]ethylamino] ethyl] -1,3-benzothiazol-2(3H)-one.

- 10 2. A method of treating chronic obstructive pulmonary disease (COPD) in a mammal, which method comprises administering a first pharmaceutical agent and a second pharmaceutical agent, wherein the first pharmaceutical agent is a compound of formula II



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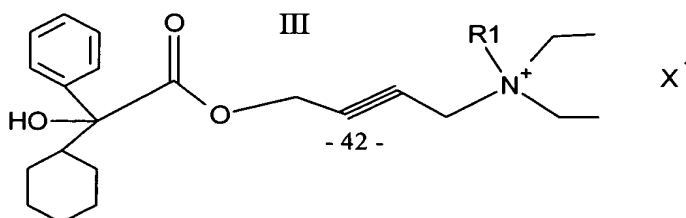
or a stereoisomer thereof, wherein

R_1 is C_1-C_6 alkyl, $-CH_2-(C_1-C_4$ alkenyl), or $-CH_2-(C_1-C_6$ alkynyl), each of which is optionally substituted with phenyl, C_1-C_4 alkoxy, or hydroxyl; and

X^- is an anion of a pharmaceutically acceptable acid; and

- 20 the second pharmaceutical agent is an Adenosine A_{2a} Receptor Agonist, a D2-Dopamine Receptor Agonist, a PDE Inhibitor, a corticosteroid, a norepinephrine reuptake inhibitor, or 4-hydroxy-7-[2-[2-[3-[2-phenylethoxy]-propylsulphonyl]ethylamino] ethyl] -1,3-benzothiazol-2(3H)-one.

- 25 3. A method of treating chronic obstructive pulmonary disease (COPD) in a mammal, which method comprises administering a first pharmaceutical agent and a second pharmaceutical agent, wherein the first pharmaceutical agent is a compound of formula III



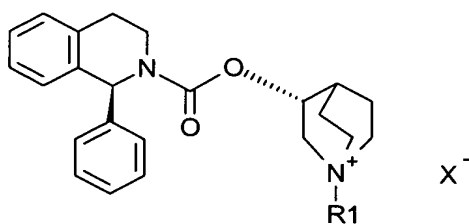
or a stereoisomer thereof, wherein

R₁ is C₁-C₆ alkyl, -CH₂-(C₁-C₄ alkenyl), or -CH₂-(C₁-C₆ alkynyl), each of which is optionally substituted with phenyl, C₁-C₄ alkoxy, or hydroxyl; and

X⁻ is an anion of a pharmaceutically acceptable acid; and

5 the second pharmaceutical agent is an Adenosine A_{2a} Receptor Agonist, a D2-Dopamine Receptor Agonist, a PDE Inhibitor, a corticosteroid, a norepinephrine reuptake inhibitor, or 4-hydroxy-7-[2-[2-[3- [2-phenylethoxy]-propylsulphonyl]ethylamino] ethyl] -1,3-benzothiazol-2(3H)-one.

10 4. A method of treating chronic obstructive pulmonary disease (COPD) in a mammal, which method comprises administering a first pharmaceutical agent and a second pharmaceutical agent, wherein the first pharmaceutical agent is a compound of formula IV



15 IV

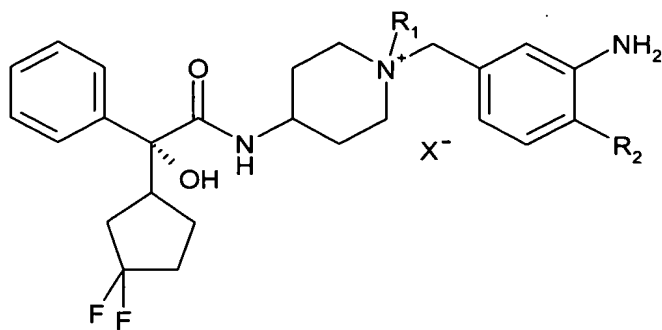
or a stereoisomer thereof, wherein

R₁ is C₁-C₆ alkyl, -CH₂-(C₁-C₄ alkenyl), or -CH₂-(C₁-C₆ alkynyl), each of which is optionally substituted with phenyl, C₁-C₄ alkoxy, or hydroxyl; and

X⁻ is an anion of a pharmaceutically acceptable acid; and

20 the second pharmaceutical agent is an Adenosine A_{2a} Receptor Agonist, a D2-Dopamine Receptor Agonist, a PDE Inhibitor, a corticosteroid, a norepinephrine reuptake inhibitor, or 4-hydroxy-7-[2-[2-[3- [2-phenylethoxy]-propylsulphonyl]ethylamino] ethyl] -1,3-benzothiazol-2(3H)-one.

25 5. A method of treating chronic obstructive pulmonary disease (COPD) in a mammal, which method comprises administering a first pharmaceutical agent and a second pharmaceutical agent, wherein the first pharmaceutical agent is a compound of formula V



V

or a stereoisomer thereof, wherein

R₁ is C₁-C₆ alkyl, -CH₂-(C₁-C₄ alkenyl), or -CH₂-(C₁-C₆ alkynyl), each of
 5 which is optionally substituted with phenyl, C₁-C₄ alkoxy, or hydroxyl;

R₂ is H or OH; and

X⁻ is an anion of a pharmaceutically acceptable acid; and

the second pharmaceutical agent is an Adenosine A_{2a} Receptor Agonist, a D2-
 Dopamine Receptor Agonist, a PDE Inhibitor, a corticosteroid, a norepinephrine
 10 reuptake inhibitor, or 4-hydroxy-7-[2-[2-[3- [2-phenylethoxy]-
 propylsulphonyl]ethylamino] ethyl] -1,3-benzothiazol-2(3H)-one.

6. The method of claim 2, 3, 4 or 5 wherein X⁻ is an anion of tartaric acid;
 hydrochloric acid; hydrobromic acid; hydroiodic acid; sulfuric acid; phosphoric acid;
 15 nitric acid; citric acid; methanesulfonic acid; CH₃-(CH₂)_n-COOH, where n is 0 to 4;
 HOOC-(CH₂)_m-COOH, where m is 1 to 4; HOOC-CH=CH-COOH; or benzoic acid.

7. The method of claim 1, 2, 3, 4 or 5 wherein X⁻ is iodide, bromide, or chloride.

20 8. The method of claim 1, 2, 3, 4 or 5 comprising administering a pharmaceutical
 composition of a compound of the formula I, II, III, IV or V.

9. The method of claim 8 wherein the pharmaceutical composition comprises
 between about 1 mg and about 1000 mg of the compound of the formula I, II, III, IV
 25 or V.

10. The method of claim 9 wherein the pharmaceutical composition comprises between about 200 mg and about 800 mg of the compound of the formula I, II, III, IV or V.
- 5 11. The method of claim 9 wherein the pharmaceutical composition comprises about 600 mg of the compound of the formula I, II, III, IV or V.
12. The method of claim 1, 2, 3, 4 or 5 wherein the compound of the formula I, II, III, IV or V is administered via inhalation or insufflation.
- 10 13. A method of treating chronic obstructive pulmonary disease (COPD) in a mammal, comprising administering a first pharmaceutical agent and a second pharmaceutical agent, wherein the first pharmaceutical agent is
- 15 (3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide;
- (3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide;
- (3R)-N-ethyl-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-3-phenylpropan-1-aminium iodide;
- 20 (3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-3-phenyl-N-propylpropan-1-aminium iodide;
- (3R)-N-benzyl-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-3-phenylpropan-1-aminium iodide;
- (3R)-N-(tert-butyl)-3-(2-hydroxy-5-methylphenyl)-N,N-dimethyl-3-phenylpropan-1-
- 25 aminium bromide;
- (3R)-3-[2-hydroxy-5-(hydroxymethyl)phenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide;
- (3R)-3-(2-hydroxyphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide;
- 30 (3S)-3-(2-hydroxyphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide;
- (3R)-3-(5-chloro-2-hydroxyphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide;

- (3R)-3-(5-bromo-2-hydroxyphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide;
- (3R)-3-[2-(acetyloxy)-5-methylphenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide;
- 5 (3R)-3-[2-(isobutyryloxy)-5-methylphenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide;
- (3R)-3-(4-fluorophenyl)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methylpropan-1-aminium bromide;
- (3R)-3-[2-hydroxy-5-(trifluoromethyl)phenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide;
- 10 (3R)-3-[2-(isobutyryloxy)-5-hydroxymethylphenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide;
- (3R)-3-{2-(acetyloxy)-5-[(acetyloxy)methyl]phenyl}-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide;
- 15 2-[(1R)-3-[diisopropyl(methyl)ammonio]-1-phenylpropyl]-4-methylbenzenolate; 1-[3-(2-hydroxy-5-methylphenyl)-3-phenylpropyl]-1-(2-methylprop-2-enyl)pyrrolidinium bromide;
- 1-[3-(2-hydroxy-5-methylphenyl)-3-phenylpropyl]-1-(3-methylbut-2-enyl)pyrrolidinium bromide;
- 20 1-allyl-1-[3-(2-hydroxy-5-methylphenyl)-3-phenylpropyl] pyrrolidinium iodide; 1-allyl-1-[3-(2-hydroxy-5-methylphenyl)-3-phenylpropyl] pyrrolidinium chloride;
- 3-(2-hydroxy-5-methylphenyl)-N,N-diallyl-N-methyl-3-phenylpropan-1-aminium iodide;
- 3-(2-hydroxy-5-methylphenyl)-N,N-diallyl-N-ethyl-3-phenylpropan-1-aminium iodide;
- 25 1-allyl-1-[3-(2-hydroxy-5-methylphenyl)-3-phenylpropyl]piperidinium chloride;
- 3-(2-hydroxy-5-methylphenyl)-N,N,N-triallyl-3-phenylpropan-1-aminium bromide;
- (3S)-3-(2-amino-2-oxo-1,1-diphenylethyl)-1-[2-(2,3-dihydro-1-benzofuran-5-yl)ethyl]-1-methylpyrrolidinium iodide;
- 30 4-(diethylmethylaminium)-2-butyryl alpha phenyl cyclohexane glycolate iodide; 3-methyl-3-quinuclidinyl 1-phenyl-2-isoindolinecarboxylate; or
- (2R)-N-[1-(6-aminopyridin-2-ylmethyl)-1-methylpiperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide iodide; and

the second pharmaceutical agent is an Adenosine A_{2a} Receptor Agonist, a D2-Dopamine Receptor Agonist, a PDE Inhibitor, a corticosteroid, a norepinephrine reuptake inhibitor, or 4-hydroxy-7-[2-[2-[3-[2-phenylethoxy]-propylsulphonyllethylamino] ethyl] -1,3-benzothiazol-2(3H)-one.

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